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Involvement of the Septum in Central Dopamine-Acetylcholine Interactions in Morphine-Treated Cats

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MEGENS, A. A. P. H. AND A. R. COOLS. *Involvement of the septum in central dopamine-acetylcholine interactions in morphine-treated cats.* PHARMACOL BIOCHEM BEHAV 18(5) 761–767, 1983.—The involvement of the septum in central dopamine-acetylcholine (DA-ACh) interactions was investigated by analysis of the behavioural effects of intracerebrally injected drugs in cats pretreated with morphine (5 mg/kg, IP). The intracerebrally evoked effects on the morphine-induced behaviour were analyzed both quantitatively (changes in the incidence of locomotor patterns) and qualitatively (changes in the stereotyped nature of the behaviour patterns). Activation of a particular subclass of dopamine receptors (DAi receptors) within the septum by means of the DAi agonist (3,4-dihydroxyphenylamino)-2-imidazoline (DPI) suppressed the effect of intraseptal injections of the cholinergic agonist carbachol. Simultaneous activation of the DAi receptors within the septum and those within the caudate nucleus produced an effect characteristics of activation of septal DAi receptors; the effect characteristic of activation of caudate DAi receptors was suppressed. Analogous results were obtained when the DAi receptors within the septum and those within the caudate nucleus were simultaneously inhibited by the DAi antagonist ergometrine. Finally, it was found that the effect of intraseptal injections of the cholinergic agonist carbachol was suppressed by inhibition of the DAi receptors within the caudate nucleus. In the latter case, the effect characteristic of inhibition of caudate DAi receptors was also suppressed. The present results indicate the existence of interactions between (1) septal ACh activity and septal DAi activity, (2) septal DAi activity and caudate DAi activity, and (3) septal ACh activity and caudate DAi activity. A mechanism of action for the observed interactions is discussed.

Septum Caudate nucleus Dopamine Acetylcholine Parkinson's disease Cat

A DISTURBANCE of a balance between dopamine (DA) and acetylcholine (ACh) within the basal ganglia, in particular the caudate nucleus, is thought to be one of the etiological factors in Parkinson's disease [4, 5, 18, 24]. However, there is still some doubt about the actual nature of the DA-ACh interactions within the caudate nucleus [6, 12, 27]. On the other hand, recent studies from our laboratory have opened the perspective that the cholinoceptive septum, which is innervated by dopaminergic fibres originating in the ventral tegmental area of Tsai [19], might play an important role in the central DA-ACh balance. For instance, increasing DA activity within the feline septum was found to produce behavioural effects that are diametrically opposite to those elicited by increasing ACh activity within the same structure [20,21]. Since the dopaminergic fibres terminating within the septum arise from cell groups that also project to the head of the caudate nucleus [14] and since the latter cell groups appear to form part of a striato-tegmental feedback loop [17], the question arises whether changing the DA activity within the head of the caudate nucleus has consequences for the DA activity in the tegmento-septal fibres. If this is indeed the case, it will be evident that the cholinoceptive septum might play an important role in the DA-ACh balance within the brain. The present study provides a first piece of evidence in favour of this hypothesis.

The various aspects of the above-mentioned hypothesis were investigated by analysis of the behavioural effects of single and combined injections of cholinergic and dopaminergic drugs into the septum and/or the head of the caudate nucleus. The experiments were performed in cats pretreated with an intraperitoneal injection of morphine because of the following reasons. In open field tests, intraseptal injections of dopaminergic drugs affect the behaviour of morphine-treated cats but generally not the behaviour of animals untreated with morphine [21]; the same holds true for intraseptal injections of cholinergic agents, although the latter ones produce a slight, but not significant change in locomotor activity [20]. Second, the morphine-pretreatment enables a distinction between intraseptally and intracaudately evoked effects since intraseptal injections of dopaminergic and cholinergic drugs affect primarily the incidence and not the sterotyped nature of the morphine-induced behaviour patterns, whereas intracaudate injections of dopaminergic drugs affect primarily the stereotyped nature of the morphine-induced behaviour patterns (cf. [11, 20, 21]). Finally, it is known that systemically administered morphine

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produces its behavioural effects in cats neither via DA or ACh receptors within the septum [22] nor via DA receptors within the caudate nucleus [11]: accordingly, the effects elicited by the chosen intracerebrally administered drugs cannot result from their putative ability to affect morphine-sensitive receptors within the brain structures selected.

In the cat, the projection regions of the ventral tegmental area in both the septum and the caudate nucleus are marked by the presence of so-called DAi receptors [7, 8, 10, 21]. Therefore, the DAi agonist (3,4-dihydroxyphenylamino)-2-imidazoline (DPI) and the DAi antagonist ergometrine were chosen as tools to change dopaminergic activity in these brain structures (cf. [3, 7, 8, 13, 25, 26, 28, 29]. The cholinergic agonist carbachol was chosen as a tool to change cholinergic activity within the septum.

METHOD

For a detailed description of the experimental conditions and procedures the reader is referred to previous reports [20, 21, 22]; only details of the experimental conditions and procedures relevant to the present experiments will be described below.

Fifty-three adult cats (2.0–3.5 kg) of both sexes were used. They were obtained from the breeding colony of the Central Animal Laboratory University of Nijmegen, and housed and fed under standard laboratory conditions. Each animal was bilaterally equipped with cannulas directed to the antero-dorsal part of the caudate nucleus (sterotaxic co-ordinates according to Snider and Niemer [23]: A 18–19, L 3–5, H 4–6) and/or the anterior part of the septum (sterotaxic co-ordinates according to Snider and Niemer [23]: A 15–19, L 0–2, H 1–6): these subdivisions of the septum and the caudate nucleus have been found previously to be most sensitive for the drugs used in the present study [11, 20, 21, 22] (cf. Figs. 3, 4). The outer and inner diameters of the double-barrelled, stainless steel cannulas were 0.8 and 0.5 mm, respectively. A two week recovery period was allowed before starting the experiments. Moreover, the cats were adapted to the injection procedure by inserting an empty needle through the cannulas into the target areas. The cats were acquainted with the experimental cage during 2 periods of 1 hr and an additional period of 0.25 hr immediately before the experiments. The cage (88×66×61 cm) was sound-proof and equipped with a ventilator producing background noise. With exception of the front window, the walls were opaque. The cage was illuminated by a bulb of 60 watts placed 61 cm above the floor; the room temperature ranged between 18–25°C.

All cats were pretreated with an intraperitoneal injection of morphine (5 mg/kg). The effects of intracerebral injections of drugs on the morphine-induced behaviour were analyzed (see below). The drugs were intracerebrally administered by means of Hamilton injection syringes (the injection flow rate was ca. 1 μl/sec). The volume injected was 0.5 μl for target sites within the septum and 5.0 μl for target sites within the caudate nucleus. All the drugs were administered bilaterally. The following agents were used: carbamylcholine hydrochloride (carbachol; Sigma), (3,4-dihydroxyphenylamino)-2-imidazoline hydrochloride (DPI; Wander), ergometrine maleate (Halewood Chemicals) and morphine hydrochloride (De Onderlinge Pharmaceutische Groothandel). The doses and the injection volumes used in this study are known to affect selectively DA receptors of the DAi type or ACh receptors of the muscarinic type within the chosen brain regions [10, 20, 21]. All the drugs were dissolved in distilled water, apart from morphine which was dissolved in saline (0.9% NaCl). The doses refer to the salts.

When animals were tested more than once, an inter-trial interval of 2 weeks was used. The experiments were performed under comparable experimental conditions. After the experiments the animals were sacrificed by means of an overdose of pentobarbital (Nembutal® or Narcovet®) and intracardially perfused with a formaldehyde solution (4–10%) containing the anticoagulant heparin (50 mg/l). The brains were sectioned along the tracks of the guide cannulas. The injection sites were localized with the help of the atlas of Snider and Niemer [23].

Behavioural Analysis

The cats were observed for 60 min after the intraperitoneal injection of morphine. Drugs were intracerebrally injected into the septum and/or the caudate nucleus 40–41 min after intraperitoneal administration of morphine. As in previous experiments [9,11], the behaviour at this time was characterized by the display of a restricted number of senseless behaviour patterns that were regularly repeated at stable frequencies. Moreover, these behaviour patterns were idiosyncratic and stereotyped [9,11]. As it has been found that intracaudate injections of dopaminergic drugs affect primarily the stereotyped nature of the morphine-induced behaviour patterns [9,11], particular attention was paid to intracerebrally evoked changes in the stereotyped nature of the behaviour patterns. The behaviour was also analyzed quantitatively (changes in incidence of locomotor patterns) since it has been found that intraseptal injections of dopaminergic or cholinergic drugs primarily affect the incidence of the morphine-induced behaviour patterns [20,21]. Single locomotor patterns were defined as: (1) discontinuous locomotion: any forward or backward movement of the animal along a minimum distance of 40 cm; (2) continuous locomotion: any forward or backward movement of the animal along a fixed distance of 80 cm; (3) discontinuous turning: any turning movement of the animal around a minimum angle of 180°; (4) continuous turning: any turning movement of the animal around a fixed angle of 360°. Both the total number of locomotor patterns during the 10 min immediately preceding the intracerebral injections (X_{pre}) and that during the 10 min immediately following the intracerebral injections (X_{post}) were determined per animal. The behaviour was not analyzed during the 2 min injection period.

The following procedure was followed for the statistical analysis of the drug-induced effects on the incidence of the locomotor patterns in order to solve the problem of the rather high degree of interindividual differences (Table 1). When the effect was an increase in the incidence of the locomotor patterns, the absolute difference in the number of locomotor patterns per animal during the pre- and post-injection periods was determined:

$$\Delta_{abs} = X_{post} - X_{pre}$$

The values obtained in this manner per test group were compared with the corresponding values for the appropriate control groups.

As the drug-induced decreases in incidence of locomotor patterns can only occur in animals showing at least some locomotor patterns during the pre-injection period, only

TABLE 1

EXPERIMENTAL DESIGN INCLUDING THE NUMBER (MEAN ± SEM) OF LOCOMOTOR PATTERNS DISPLAYED DURING THE PRE- AND POST-INJECTION PERIODS (X_{pre} AND X_{post}) AND THE PERCENTAGES OF ANIMALS CHANGING THEIR STEREOTYPED BEHAVIOUR AFTER THE INTRACEREBRAL INJECTIONS (ΔS; ALL ANIMALS SHOWED STEREOTYPED BEHAVIOUR BEFORE THE INJECTIONS)

group (trial)	n	treatment	dose* (μg)	$Mean_{pre}$	$Mean_{post}$	ΔS
1 (1)	7	i.s. CARB	1	56 ± 36	122 ± 43	0
1 (2)	7	i.s. CARB	1	76 ± 34	162 ± 42	0
2 (1)	11	i.s. CARB i.s. AQUA	1 0.5 μl	46 ± 23	113 ± 30	0
2 (2)	11	i.s. CARB i.s. DPI	1 5	71 ± 17	109 ± 26	0
3 (1)	8	i.s. CARB i.c. AQUA	1 5 μl	22 ± 9	100 ± 31	0
3 (2)	8	i.s. CARB i.c. ERGO	1 10	46 ± 24	74 ± 35	0
4 (1)	15 [9]†	i.s. DPI§	10	20 ± 5 (32 ± 6)‡	9 ± 2 (13 ± 3)‡	0
5 (1)	16 [8]†	i.s. DPI i.c. DPI 10	10 10	46 ± 16 (91 ± 21)‡	31 ± 10 (58 ± 16)‡	0
6 (1)	10 [4]†	i.s. ERGO§	10	35 ± 15 (85 ± 15)‡	48 ± 15 (97 ± 16)‡	0
7 (1)	11 [8]†	i.s. ERGO i.c. ERGO	10 10	93 ± 34 (126 ± 41)‡	92 ± 28 (125 ± 31)‡	0

*Injected volume was 0.5 μl for target sites within the septum and 5.0 μl for target sites within the caudate nucleus; all injections were given bilaterally.

†Number of animals with $X_{pre} \geq 10$ (used for calculation of Δ_{rel}: see text).

‡Data from animals with $X_{pre} \geq 10$ (used for calculation of Δ_{rel}: see text).

§Control injections of distilled water into the caudate nucleus were given to group 3; as these injections were ineffective (see text), which is consistent with earlier reported data [11], control injection of distilled water into the caudate nucleus were not given to groups 4 and 6.

Abbreviations: i.c.=intracaudate; i.s.=intraseptal; AQUA=distilled water; CARB=carbachol; DPI=(3,4-dihydroxyphenylamino)-2- imidazoline; ERGO=ergometrine.

animals with at least 10 locomotor patterns during the pre-injection period were included in the statistical analysis of drug-induced decreases. As a decrease measured by the variable Δ_{abs} would be limited by the pre-injection value X_{pre} and, furthermore, these pre-injection values differed considerably between animals (see Table 1), the drug-induced decreases were measured by the relative difference Δ_{rel}, i.e., the difference between pre- and post-injection values summed:

$$\Delta_{rel} = \frac{X_{post} - X_{pre}}{X_{post} + X_{pre}} \times 100\% \ (X_{pre} \geq 10)$$

The resulting values were averaged per test group and compared with the corresponding values for the appropriate control group.

All statistical tests were two-tailed. Because of the high inter-individual variability, non-parametric statistics were applied. For related groups, the Wilcoxon matched pairs signed rank test was used in contrast to the Mann-Whitney U test, which was used for comparing independent groups.

Procedure

Four experiments were conducted. In the first experiment, the consistency in time of the effect of intraseptal carbachol was investigated by giving intraseptal injections of the cholinergic agonist in 2 separate trials, 2 weeks apart (Table 1: group 1). In the second experiment, the ability of intraseptal DPI to suppress the effect of intraseptal carbachol was investigated by giving in a first trial single intraseptal injections of carbachol and in a second trial, 2 weeks later, combined intraseptal injections of carbachol and DPI (Table 1: group 2). In the third experiment, interactions between DAi activity within the septum and DAi activity within the caudate nucleus were investigated by comparing (1) the effects of single intraseptal injections of DPI with those of combined injections of DPI into both the septum and the caudate nucleus (Table 1: groups 4 and 5), and (2) the effects of single intraseptal injections of ergometrine with those of combined injections of ergometrine into both the septum and the caudate nucleus (Table 1: groups 6 and 7). In the fourth experiment, interactions between ACh activity within the septum and DAi activity within the caudate nucleus were investigated by comparing the effects of single intraseptal injections of carbachol given in a first trial with those of combined injections of carbachol into the septum and ergometrine into the caudate nuclues (Table 1: group 3).

RESULTS

Table 1 gives a summary of the experimental design including the values (mean±SEM) for the number of locomotor patterns displayed during the pre- and post-injection

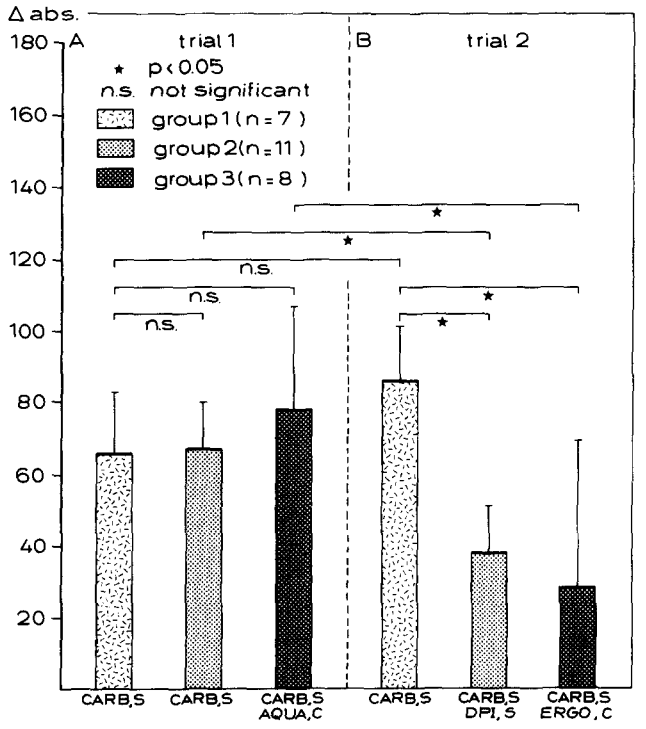

FIG. 1. Behavioural effects elicited by intraseptal (s) and/or intracaudate (c) injections of carbachol (CARB, 2×1 μg), DPI (2×5 μg), ergometrine (ERGO, 2×10 μg) and distilled water (AQUA, 2×5 μl) in cats pretreated with morphine (5 mg/kg). Drugs were administered in 2 separate trials, 2 weeks apart. Values for Δ_{abs} (mean±SEM) are given for each drug treatment.

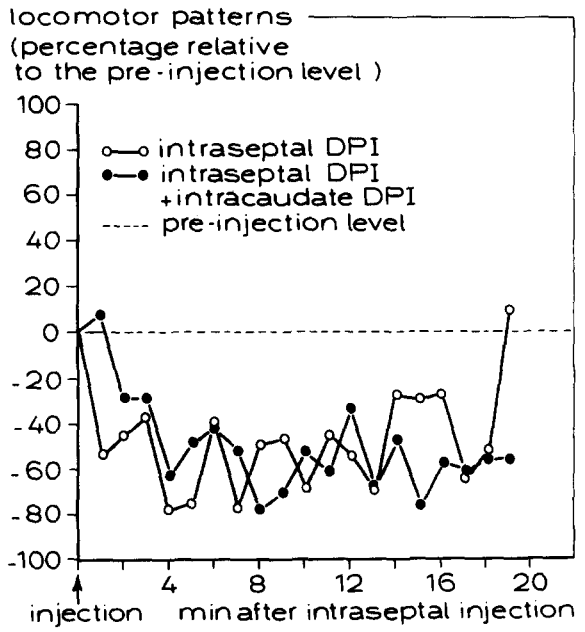

FIG. 2. Time-dependent development of changes in the incidence of morphine-induced locomotor patterns elicited by intracerebral injections of (1) DP (2×10 μg, n=9) into the septal nuclei, and (2) DPI (2×10 μg, n=8) into the septal nuclei in combination with DPI (2×10 μg) into the caudate nucleus. The number of locomotor patterns scored per animal per minute is expressed as percentage of the total number of locomotor patterns scored for each individual animal during 10 min immediately preceding and 19 min immediately following the local injection. Presented are mean values of these percentages averaged over the testgroup and expressed as percentages of the pre-injection level. Note that a 19 min post-injection period was used in contrast to the 10 min post-injection period used for the calculations of Δ_{abs} and Δ_{rel}.

periods in the various experiments. In addition, Table 1 gives the percentages of animals displaying stereotyped behaviour during the pre- and post-injection periods.

Effects of Intraseptal Carbachol

Intraseptal carbachol did not affect the stereotyped nature of the behaviour patterns, but did produce an increase in the incidence of morphine-induced locomotor patterns (Table 1: group 1, trials 1 and 2). When measured by the variable Δ_{abs}, the magnitude of this carbachol-induced effect was comparable across both trials (Fig. 1A and B: group 1). Thus, the effect of carbachol was consistent in magnitude when the drug treatment was repeated 2 weeks later.

Effects of Intraseptal DPI in Combination with Intraseptal Carbachol

In neither trial did intraseptal carbachol affect the stereotyped nature of the behaviour patterns (Table 1: group 2). Again, it did produce an increase in the incidence of the morphine-induced locomotor patterns in the first trial, as measured by the variable Δ_{abs} (Fig. 1: group 2; cf. Table 1). This effect of carbachol was comparable in magnitude with that reported above for group 1 in the first trial (Fig. 1A: cf. groups 1 and 2). In contrast, the effect of carbachol in the second trial was significantly reduced in magnitude both when compared with that obtained for the same animals in the first trial (Fig. 1A and B: group 2) and when compared with that obtained for group 1 in the second trial (Fig. 1B: cf. groups 1 and 2). In other words, intraseptal injections of DPI suppressed the effect of carbachol on the response to morphine.

Interaction Between DAi Activity Within the Septum and DAi Activity Within the Caudate Nucleus: Effects of DPI

Group 4 received single injections of the DAi agonist DPI into the septum, whereas group 5 received simultaneous injections of DPI into both the septum and the caudate nucleus. In neither group did DPI affect the stereotyped nature of the behaviour patterns (Table 1: groups 4 and 5). However, the single injections of DPI into the septum produced a decrease rather than an increase in the incidence of the morphine-induced locomotor patterns, as indicated by the values for X_{pre} and X_{post} in Table 1, group 4. Therefore, the variable Δ_{rel} was used for the statistical evaluation of this effect. The value (mean±SEM) of Δ_{rel} thus obtained for group 4 ($\Delta_{rel}=-35\pm15\%$) was not different from that obtained for group 5 ($\Delta_{rel}=-29\pm9\%$) after injection of DPI into both the septum and the caudate nucleus. Figure 2 illustrates the time course of the drug-induced effects for both group 4 and group 5. The additional intracaudate injections of DPI

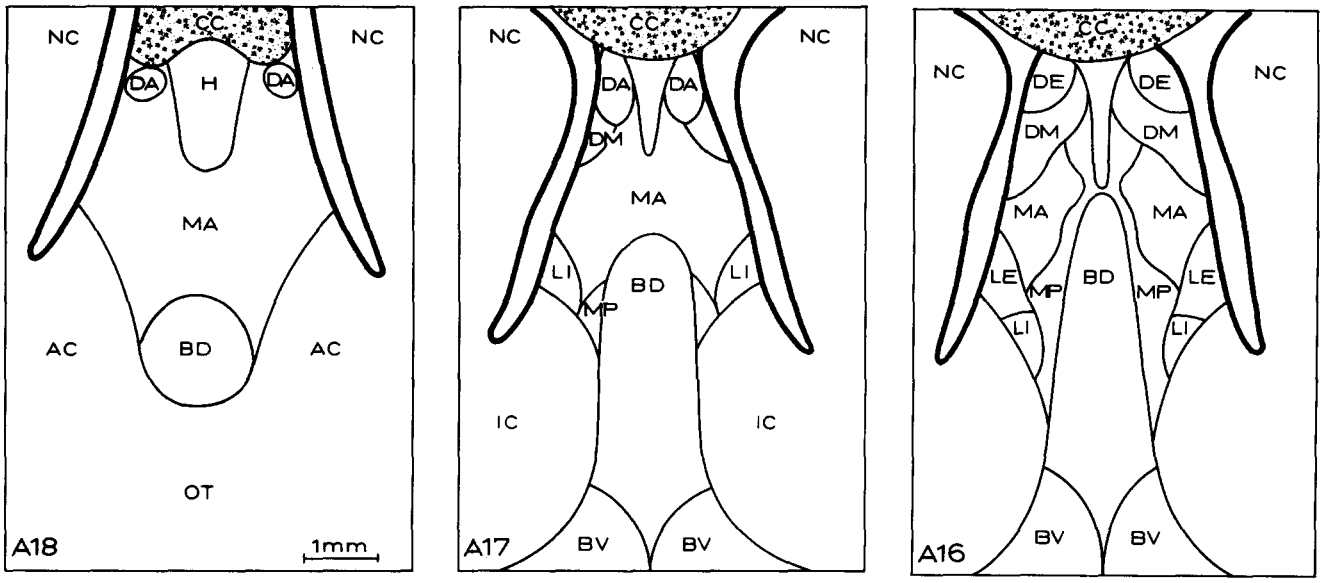

FIG. 3. Three transversal sections of the septum in the cat (sterotaxic co-ordinates: A16–A18); the effective sites were localized within the nucleus septalis medialis (MA). Abbreviations: DE, DM, LE, MA and MP=nuclei of the septum; Ac=nucleus accumbens; BD and BV=nuclei of the diagonal band of Broca; IC=islands of Calleja; NC=nucleus caudatus.

given to group 5 did apparently not affect the magnitude of the effect of the intraseptal injections of DPI. On the other hand, the previously reported potentiation of morphine-induced behaviour by intracaudate DPI [11] was absent and, consequently, suppressed by the simultaneous injections of DPI into the septum.

Interaction Between DAi Activity Within the Septum and DAi Activity Within the Caudate Nucleus: Effects of Ergometrine

Group 6 received intraseptal ergometrine, whereas group 7 received simultaneous injection of ergometrine into both the septum and the caudate nucleus. In neither group was the stereotyped nature of the behaviour patterns affected by the intracerebral injections. Moreover, as indicated by the values of X_{pre} and X_{post} in Table 1 (group 6), the incidence of the morphine-induced locomotor patterns was hardly affected by the single intraseptal injections of ergometrine. Combined injections of ergometrine into both the septum and the caudate nucleus also failed to produce significant changes in the incidence of the locomotor patterns (Table 1: group 7). The values of Δ_{abs} and Δ_{rel} obtained for group 6 ($\Delta_{abs}=14\pm6$ and $\Delta_{rel}=6\pm9\%$) were not different from those obtained for group 7 ($\Delta_{abs}=-1\pm20$ and $\Delta_{rel}=6\pm15\%$). In other words, the intracaudate injections of ergometrine did not significantly affect the response of cats to intraseptal injections of ergometrine. On the other hand, the earlier reported effect of intracaudate injections of ergometrine, i.e., the replacement of stereotyped behaviour patterns by normal ones [11], was absent and, consequently, suppressed.

Interaction Between DAi Activity Within the Caudate Nucleus and ACh Activity Within the Septum

The animals received intraseptal injections of carbachol in 2 separate trials, 2 weeks apart. The carbachol treatment was combined with simultaneous intracaudate injections of distilled water in the first trial (Table 1: group 3, trial 1) and with intracaudate injections of ergometrine in the second trial (Table 1: group 3, trial 2). In neither of both groups did the intracerebral injections affect the stereotyped nature of the behaviour patterns. In the first trial, carbachol produced an increase in the incidence of the morphine-induced locomotor patterns that was comparable in magnitude with those obtained for group 1 and group 2 after single intraseptal injections of carbachol in the first trial (Fig. 1A: cf. groups 1, 2 and 3). The additional injections of distilled water in the caudate nucleus did apparently not affect the magnitude of the carbachol effect. In contrast, the effect of carbachol in the second trial was significantly reduced in magnitude by intracaudate ergometrine, both when compared with that observed in the same group of animals in the first trial (Fig. 1A and B: group 3) and when compared with that obtained for group 1 after single intraseptal injections of carbachol in the second trial (Fig. 1B: group 1 and group 3). Moreover, the earlier reported effect of single intracaudate injections of ergometrine, i.e., the replacement of stereotyped behaviour patterns by normal behaviour patterns [11], was absent and, consequently, suppressed by the simultaneous intraseptal injection of carbachol.

Localization of Injection Sites

The injection sites were located within the anterior part of the septum (stereotaxic co-ordinates: A 16.0–18.0, L 0.0–2.0, H 1.0–5.5 [23] and within the anterodorsal part of the caudate nucleus (stereotaxic co-ordinates: A 17.5–19.5, L 2.8–4.5, H 3.0–7.0 [23] (see also Figs. 3, 4). No major signs of tissue damage were observed apart from a small region of degenerated tissue just around the cannulas and the injection sites.

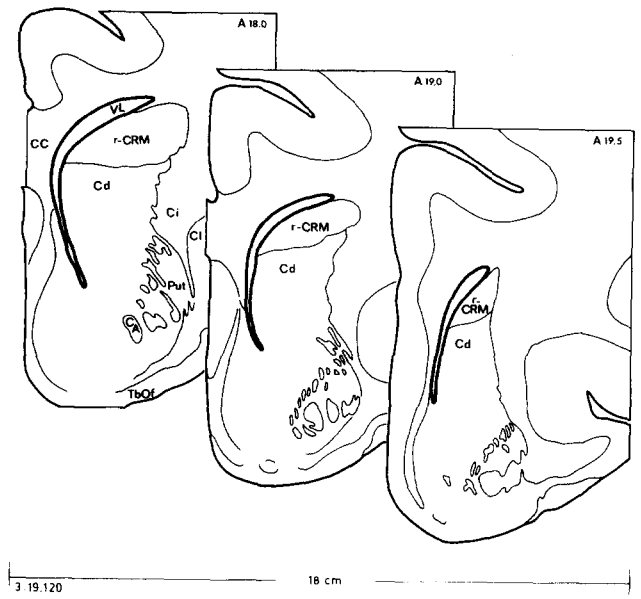

FIG. 4. Three sections of the caudate nucleus in the cat (sterotaxic co-ordinates: A18–19.5); the effective sites were located within nucleus caudatus, caput anterodorsalis (r-CRM). Abbreviations: VL=ventriculus lateralis; CC=corpus callosum; Cd=nucleus caudatus; Ci=capsula interna; Cl=claustrum; Acb=nucleus accumbens; CA=commissura anterior; Tbof=tuberculum olfactorium.

DISCUSSION

In the present study, the behavioural effects of single or combined injections of cholinergic and/or dopaminergic drugs into the anterior part of the septum and/or the antero-dorsal part of the caudate nucleus were analyzed. As the specificity of the chosen intracerebral drug treatments has been extensively discussed in previous reports [10, 11, 20, 21, 22], this will not be a subject of the present discussion. However, from the earlier reported data which were collected in studies using a similar experimental paradigm, it can be stated that (1) the intraseptal or intracaudate injections of distilled water (the vehicle used in the present study) in animals receiving a systemic injection of morphine (5 mg/kg, IP) 40 min earlier remained ineffective [11, 20, 21], (2) the intraseptal injections of carbachol activated muscarinic ACh receptors within the septum [20], (3) the intraseptal injections of DPI and ergometrine, respectively, activated and blocked DA receptors of the DAi type within the septum [21], (4) the intracaudate injections of DPI and ergometrine respectively activated and blocked DA receptors of the DAi type within the caudate nucleus [11], and (5) morphine-sensitive receptors were not involved in the effects elicited by the intraseptally and/or intracaudately administered drugs [11, 20, 21]. Hence, the observed effects are discussed in terms of interactions between these septal and caudate neuronal systems.

The present results indicate the existence of (1) interactions between DAi activity and ACh activity within the septum itself, (2) interaction between DAi activity within the septum and DAi activity within the caudate nucleus, and (3) interaction between ACh activity within the septum and DAi activity within the caudate nucleus. First, the interactions within the septum itself are discussed. The finding that the behavioural effect of intraseptal injections of the cholinergic agonist carbachol was reduced in magnitude by intraseptal injections of the DAi agonist DPI indicates the existence of an antagonistic interaction between septal ACh activity and septal DAi activity. These data complement the earlier reported data that intraseptal injections of DAi agonists produced a decreased incidence of morphine-induced locomotor patterns whereas intraseptal injections of cholinergic agonists produced an increased incidence of these patterns [20,21]. The antagonistic interaction between septal ACh activity and septal DAi activity cannot be ascribed to a cholinergic-induced inhibition of septal DAi activity, since intraseptal injections of cholinergic agonists produce an increased incidence of morphine-induced locomotor patterns, whereas intraseptal injections of the DAi antagonist do not affect their incidence [20,21]. Nor can the antagonistic interaction be ascribed to a dopaminergic-induced inhibition of septal ACh activity since intraseptal injections of DAi agonists produce a decreased incidence of morphine-induced locomotor patterns whereas intraseptal injections of cholinergic antagonists fail to affect their incidence [20,21]. Hence, it is argued that the septal DAi system and the septal ACh system are not serially linked but, instead, converge on a yet unknown common output system of the septum upon where they exert mutually opposite actions.

The present results also provide evidence for the existence of interactions between DAi activity within the septum on one hand and DAi activity within the caudate nucleus on the other hand:

(1) Simultaneous activation of the DAi receptors within the septum and those within the caudate nucleus resulted in an effect characteristic of activation of the septal DAi receptors, namely a decrease in the incidence of the morphine-induced locomotor patterns (cf. [21]). The effect known to occur after activation of the caudate DAi receptors, i.e., a potentiation of the morphine-induced behaviour [11], was completely suppressed.

(2) Simultaneous inhibition of the DAi receptors within the septum and those within the caudate nucleus resulted in an effect characteristic of inhibition of the septal DAi receptors: neither the incidence nor the stereotyped nature of the morphine-induced locomotor patterns was affected (cf. [21]). The effect known to occur after inhibition of the caudate DAi receptors, i.e., the replacement of stereotyped behaviour patterns by normal ones [11], was suppressed.

The finding that intraseptal injections of the DAi antagonist ergometrine, which are ineffective per se [21], suppressed the effect of intracaudate injections of ergometrine indicates that the latter effect is, at least partly, mediated via an enhanced DAi activity within the septum. The finding that intraseptal injections of the DAi agonist DPI suppressed the effect of intracaudate injections of DPI suggests exactly the opposite: the latter effect is, at least partly, mediated via a decreased DAi activity within the septum. Septal DAi activity is apparently inversely related to caudate DAi activity. This result is in line with the existence of a "feed-back" loop between the caudate nucleus and the ventral tegmental area that controls the activity both in the dopaminergic fibres terminating within the caudate nucleus and in the dopaminergic fibres terminating within the septum (see Introductory paragraphs). Changes in caudate DAi activity trigger this "feed-back" mechanism and, consequently, result in opposite changes in septal DAi activity. Such a

"feed-back" loop mechanism, being in fact a "feed-forward" mechanism, offers an explanation of the observation that effects caused by changing caudate DAi activity were suppressed by changing DAi activity within the septum; further research is required to confirm the latter hypothesis.

In view of the observed interactions between (1) caudate DAi activity and septal DAi activity, and (2) septal DAi activity and septal ACh activity, one might expect interactions between caudate DAi activity and septal ACh activity. Indeed, the present results indicate such an interaction between both neuronal systems: (1) the intracaudate injections of ergometrine antagonized the effects of simultaneous intraseptal injections of carbachol, and (2) the intraseptal injections of carbachol suppressed the effects of simultaneous intracaudate injections of ergometrine. These results fit in with the hypothetical mechanism of action mentioned above.

In general, the present data indicate that septal DAi activity and septal ACh activity are modulated by dopaminergic activity within the caudate nucleus and suggest an important role of the septum in the central DA-ACh balance. In this respect, the present study provides further evidence for the earlier reported notion that there exists a functional interaction between the caudate nucleus and the cholinergic septo-hippocampal system (cf. [1, 2, 15, 16]). It will be evident that this opens new perspectives for understanding the mechanism of action underlying the therapeutic efficacy of anticholinergics in patients with dysfunctioning dopaminergic systems within the brain, i.e. patients with psychomotor disorders such as Parkinson's disease.

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